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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,216	07/02/2001	Jennifer L. Hillman	PF-0181-2 CON	3495

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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/28/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/898,216	HILLMAN ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20,23,28 and 29* is/are pending in the application.

4a) Of the above claim(s) *3-16,20,23,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the restriction requirement was improper and that the search for the additional inventions would not pose undue burden on the examiner. This is not found persuasive because the elected invention is drawn to an isolated polypeptide, of which already requires a search in an ever expanding and updated database of protein and polypeptide sequences. Any search for additional inventions, such as for antibodies, nucleic acids, or methods associated with the peptide of group I would require searching in several other databases which are not overlapping nor co-extensive with the search for the peptide of group I. Furthermore, the classification of the different inventions on its own, characterizes the inventions as being distinct and separate. As such, the examination of the additional groups, besides that of group I, would prove to be a burdensome search because not only would it require searching multiple databases, it also requires searching in multiple and different classes and subclasses.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 4,5,19,21,22,24-27,30-45 were canceled upon filing of the request for continuation application. Therefore, claims 1-3, 6-18, 20, 23, and 28-29 are pending, claims 3-16, 20, 23, and 28-29 are withdrawn from consideration as being drawn to a non-elected invention, and claims 1-2 and 17-18 are examined on the record.

3. This application contains claims 3-16, 20, 23, and 28-29 drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

4. The Information Disclosure Statement filed 1/16/02 (paper no. 5) is acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 1-2 and 17-18 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility. The disclosed utilities for the IMP comprising the amino acid sequence of SEQ ID No: 1, variants having at least 90% identity to SEQ ID No: 1, and fragments of SEQ ID No: 1 include the diagnosis, prognosis and treatment of disease. However, neither the specification nor any art of record teaches what the IMP is, how it functions, or a specific and well-established utility for any of the variants or fragments claimed. Furthermore, the specification does not teach a relationship to any specific disease or establish any involvement in the etiology of any specific disease. Additional disclosed utilities for IMP include the treatment of disorders associated with ion-transport, the

identification of agents which can modulate its activity, the diagnosis of patients suffering from diseases associated with IMP, through the monitoring of IMP levels or expression. The asserted utility of IMP is based on the assertion that IMP (SEQ ID No: 1) is structurally similar to human stomatin, and stomatin like proteins such as MEC-2 and UNC24 from *C. elegans,* Z79701, a protein from *M. tuberculosis,* a membrane protein from *M. jannaschii*, and that in particular, IMP shares structural similarities in certain amino acid segments to stomatin, MEC-2, UNC24, Z79701, and a membrane protein from *M. jannaschii.* Further, the specification teaches that IMP "appears to play a role in the regulation of ion channels".

The specification further proposes, based on sequence similarity to stomatin, that IMP will have similar biological effects and activities (page 27, line 5-13). However, evidence based on protein sequence homology does not alone permit extrapolation to an isolated amino acid's biological function or use thereof. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of

maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Thus, despite the segmental homology between stomatin and stomatin like proteins, wherein the homology is based on local and segment based

identity, there still is a clear difference between imp and stomatin andstomatin-like proteins and it cannot be predicted, based on the information in the specification, what affect this difference has on the function of the protein. Further even if the polypeptide of SEQ ID No: 1 is structurally similar to stomatin and stomatin-like proteins, neither the specification nor any art of record teaches what the polypeptide is, what it does, nor teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active as claimed in a pharmaceutical composition.

In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation

via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Scott et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 67%-70% dissimilarity, to stomatin, the function of the SEQ ID NO:1 polypeptide could not be predicted, based on sequence similarity with stomatin, nor would it be expected to be the same as that of stomatin.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide variants and fragments thereof. Because the claimed invention is not supported by a specific or asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 1-2 and 17-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID No: 1 and therefore the written description is not commensurate in scope with the claims which read on variants which as claimed, include naturally occurring polypeptides that are at least 90% identical to SEQ ID No: 1, and biologically active and immunogenic fragments of SEQ ID No: 1.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and or encoded variants/fragments and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a

reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Furthermore, although drawn specifically drawn to the DNA art the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Support for variants and fragments of SEQ ID No: 1 is provided in the specification on page 15 lines 17-20, and on page 3, lines 14-15. However, no disclosure, beyond the mere mention of variants and or fragments is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an isolated IMP polypeptide molecule having an amino acid sequence of SEQ ID No: 1 meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

9. Claims 1 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Wakefield TW *et al* (US Patent 5534619). Claims 1 and 17 are drawn to a polypeptide comprising an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID No: 1 and a composition that comprises an pharmaceutical carrier. Wakefield *et al* teach a fragment of SEQ ID No: 1, which is to be administered with a pharmaceutically acceptable carrier. Because any fragment is potentially immunogenic given the correct dosage and concentration, the protein fragment disclosed by Wakefield *et al*, in the absence of evidence to the contrary would be immunogenic.

10. Claims 1 and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Zhang *et al* (US Patent 5670483). Claims 1 and 17 are drawn to a polypeptide comprising an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID No: 1 and a composition that comprises an pharmaceutical carrier. Zhang *et al* teach a fragment of SEQ ID No: 1, which is to be administered with a pharmaceutically acceptable carrier. Because any fragment is potentially immunogenic given the correct dosage and concentration, the protein fragment disclosed by Zhang *et al*, in the absence of evidence to the contrary would be immunogenic.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
December 27, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600